REMARKS

Reconsideration of this patent application is respectfully requested in view of the foregoing amendments, and the following remarks.

The claims have been amended in order to provide a new set of claims directed to a therapeutic method for pathologies specifically of the posterior segment of the eye.

The new claim set presents claim 11 as main independent claim. With respect to the set of claims on file, the Applicant has re-introduced the method for SLN preparation in the independent claim 11, traversing the Examiner's withdrawal of former claims 8-10 because this permits emphasizing the differences in resulting SLNs with respect to the prior art.

The Applicants traverse the withdrawal of process claims 8-10 applied by the Examiner in the last Office Action because the SLN preparation method represents a limitation to the therapeutic method under examination and it has not been independently claimed. As a matter of fact, the SLN preparation is disclosed in the prior art (EP 526666) as clearly mentioned in the present Patent Application (see for example page 2, line 25

of the PCT Application).

The amendment to refer to SLN preparation method in the independent therapeutic method claim 11, represents in any case a limitation to the therapeutic method (i.e. that Solid Lipid Nanoparticles have only to be prepared according to the Applicant's own method) and should be considered to reduce the scope of protection of the claim under examination.

This is necessary for two reasons: the first one is that only by using the proprietary SLN as a vehicle, a drug can reach the posterior segment of the eye, and secondly, to differentiate between the SLN used in this method and those used in the prior art methods.

In fact, without a reference to the method for their preparation, SLNs (Solid Lipid Nanoparticles) represents only an abbreviation. Only by the limitation in the independent claim, different results in terms of therapeutic efficacy and targeting (i.e. reaching the posterior segment of the eye) becomes understandable with respect to nano- or micro- lipid emulsions of the prior art.

As already stated above, the results of the presently

claimed therapeutic method can be obtained only with the SLNs prepared according to the Applicant's proprietary method. Therefore, this new set of claims which is filed herein and, in the remarks set forth below, the correspondence between the newly added claims and the set of claims (formerly on file) is provided.

Each of claims 1 to 10 and 12 to 21 have been cancelled without prejudice.

With regard to the claims filed herewith, support for amended Claim 11 corresponds to claim 11 as previously filed, and as amended to include the SLN preparation method (corresponding to former claim 8), and the limitation to "ophthalmic diseases of the posterior segment of the eye" for which support is found on page 5, line 23-24 of the present Specification.

New claim 22 corresponds to former claim 9.

New claim 23 corresponds to former claim 10.

New claim 24 corresponds to former claim 21.

New claim 25 corresponds to former claim 7.

New claim 26 corresponds to former claim 12.

New claim 27 corresponds to former claim 13.

New claim 28 corresponds to former claim 4.

In reply to the Examiner's objection, the following is provided.

Regarding informalities, Claims 12-13, now claims 26 and 27, have been amended according to the Examiner's suggestion.

Regarding the 35 USC § 112 rejection, the Applicant has limited independent claim 11 to a therapeutic method for diseases of the posterior segment of the eye, which represents the most relevant scientific finding behind the present Invention when carried out with the SLNs of the present invention.

Data are shown in Examples 2-3, where intravenous (through the marginal ear vein of rabbits) administration of gentamicin-loaded SLNs of the invention (in two different doses of: 1.5 mg /kg or 2 mg/kg) has been compared to other intravenously administered drug-compositions (Gentomil ®).

The results shown at pages 6-7 under the marking a) have been obtained with gentamicin-loaded SLNs, while b) refers to a commercial composition, both administered intravenously (through

the marginal ear vein of rabbits). It can be observed that loading of the active principle into SLNs allows an ocular drug distribution also in the posterior segment of the eye (as determined by the presence of gentamicin especially in the retina) while the drug in the known composition is present at only very low level in the vitreous fluid and is never found in the retina.

Similar results are obtained with topical ocular administration of SLNs (examples 4-5) according to the invention and Genticol ®, a commercial preparation for ocular topical administration. Again, the known composition shows to be unsuitable for reaching the posterior segment of the eye (vitreous fluid and retina), where, in fact, the drug is absent or present only in traces (see results on pages 8-9).

The posterior segment is defined as the back two-thirds of the eye that includes the anterior hyaloid membrane and all of the optical structures behind it: the vitreous humor, retina, choroid, and optic nerve. On the anterior side of the lens is the aqueous humour which is bounded on all sides by the lens, ciliary body, suspensory ligaments, and by the cornea.

Therefore the Applicant submits that all pathologies of the posterior segment of the eye, which are of course pharmacologically treatable, are enabled by the present Invention, because independently from the active principle loaded into the SLNs, which can be both a water-soluble or water-insoluble drug (see page 5, lines 27-29), SLNs allow any active principle to be driven to the posterior segment of the eye, as a pure tool for drug delivery.

This is true for active principles not yet known for the treatment of pathologies of the posterior segment of the eye which should become available in the near future. An example of this further therapeutic indication is the use of Bevacizumab for the treatment of Macular Senile Degeneration for which, unfortunately, only intravitreal administration is presently available.

Of note, the present invention has the advantage that it provides means for eliminating "risky" intravitreal injections by providing a more friendly administration without collateral effects.

For all these reasons, the present Specification and all the

claims are in complete compliance with all the requirements of 35 U.S.C. 112. Withdrawal of this ground of rejection is respectfully requested.

With regard to the rejection under 35 USC § 102, the Examiner states that *Amselem (US 5,662,932)* discloses SLNs comprising pharmaceutically active principles.

The Applicant replies that *Amselem* does not teach SLNs, and that this term refers only to the Solid Lipid Nanoparticles of the present invention, where the method to obtain them is also described and now claimed in independent method claim 11.

Amselem teaches drug-loaded solid emulsions for intraocular administration (Example 6 and 17). The Applicant teaches nanoparticles.

Amselem furthermore teaches how to prepare solid "nanoemulsions": these are prepared, contrary to the present invention, by dissolving lipids and emulsifiers in solvents such as diethylether, dichloromethane (Examples 1, 2, 4, 6, 8, 13, 14, 22) chloroform (Examples 12 and 16) and methanol (Example 16). These solvents are toxic and even after their evaporation, toxic

residues are left within the particle composition.

The Applicant has, contrary to the teaching of *Amselem*, limited claim 11 to SLNs prepared according to the proprietary method, where toxic solvents are NOT used.

In the method of the present invention, described from page 2, line 27 to page 3, line 9, the Solid Lipid Nanoparticles are prepared from a warm microemulsion. Indeed the lipids are melted to have them liquid and to prepare the warm microemulsion, whose nanodrops are so small that the microemulsion is transparent. After dispersion in cold water of the warm microemulsion, Solid Lipid Nanoparticles are obtained, being the solidified nanodrops. SLNs of the present invention are then washed with water (claim 11 step c) and page 3 line 4-6 and this allows the removal of water soluble components possibly not uptaken within the Solid Lipid Nanoparticles.

Amselem's nanoemulsions are disclosed to be not solid at 37°C (see col. 5, line 13-25): in fact, by definition, emulsions refer to a mixture of two or more immiscible (unblendable) liquids where one liquid (the dispersed phase) is dispersed in the other (the continuous phase).

Further confirmation is provided by the fusion point of one of the lipid used by *Amselem*, tricaprin (glycerol tridecanoate) = 31.5 C˚. Such a fusion point means that at the body temperature, the lipid is molten. On the contrary, SLNs of the present invention are SOLID at 37˚C .

Therefore, as already stated above, it is essential to specify that the independent therapeutic method claim 11, is carried out by Solid Lipid Nanoparticles prepared according to the Applicant's own method, reducing the scope of protection of the claim under examination.

This is necessary for at least two reasons: the first one is that only by using the proprietary SLN as a vehicle, a drug can reach the posterior segment of the eye (this result being only obtained with the SLN prepared according to the Applicant's own method described for example in *EP 526,666B1*) and secondly, to differentiate between the SLN used in this method and those used in the prior art methods.

In fact, without a reference to the method for their preparation, SLNs (Solid Lipid Nanoparticles) represents only an abbreviation. Only by the limitation in the independent claim, different results in terms of therapeutic efficacy and targeting

(i.e. reaching the posterior segment of the eye) becomes understandable with respect to nano- or micro- lipid emulsions of the prior art.

Last but not least, the most important difference between *Amselem* and the present invention, relevant for the therapeutic method of claim 11, beside the SLNs composition and preparation, is that *Amselem's* nanoemulsions do not achieve the presently shown results: in fact *Amselem* doesn't teach reaching the posterior segment of the eye by topical administration of the nanoemulsions-containing drugs.

In fact *Amselem* teaches only that Intra-Ocular Pressure (IOP) can be lowered by topical administration, but this effect (which is actually minimal) does not require targeting of the drug to the posterior segment of the eye, where the retina is located.

As a matter of fact, *Amselem* teaches how to treat IOP, which is only associated with glaucoma and whose reduction alleviates optical nerve damage, but does not teaches how to treat pathologies of the posterior segment of the eye, such as glaucoma. In fact glaucoma is a disease of the optic nerve, in

which the nerve cells in the front of the optic nerve (the ganglion cells) die.

Reduction of IOP is, differently from glaucoma and other pathologies of the posterior segment of the eye, usually achieved by treating topically the anterior segment of the eye (i.e. the cornea and the aqueous fluid which is in the anterior chamber of the eye) while treatment of glaucoma requires the drug to reach the optic nerve in the posterior segment of the eye (close to the retina).

It follows that *Schwartz (US 4,904,649)* teaches neither how to administer drugs to the posterior eye, nor how to treat glaucoma, contrary to the Examiner's statement.

The same is true for *Amselem*, in fact both prior art disclosures achieves the same results as described in *Schwartz (US 4,904,649)* i.e. lowering of IOP with topical administration to the conjuntiva (anterior fragment of the eye) with a common ocular preparation (eye-drops) comprising dexamethasone and epinephrine, which has effect through the cornea in the anterior face of the eye.

This has been confirmed also in the experimental part of the present invention drugs with prior art eye-drops, which, in fact, have been shown not to be able to reach the posterior segment of the eye.

Therefore, the present invention, as claimed in claim 11 and in depending claims, is novel over *Amselem* and over *Schwartz*.

Regarding the rejections under 35 USC § 102 and under 35 USC § 103, the Examiner states that *Cavalli*, alone or in combination with *Schwartz*, anticipates or renders obvious the present invention because it motivates the skilled person to put together different active principles into the SLN of the present invention and to achieve the particle size diameter disclosed in the present invention.

In the Applicant's view the particle size has only a limited effect on the peculiar properties of the SLNs and this limitation does not characterize the invention with regard to the result achieved by the therapeutic method of the present invention. In response, the Applicant has cancelled claims related to SLN size.

The main property of this therapeutic method, based on the SLNs preparation claimed (described in the Specification on page 6, Example 1) is that they surprisingly and unexpectedly reach the posterior segment of the eye with an effective amount of the drug to achieve this therapeutic effect.

Cavalli shows that tobramicin in SLNs is found after administration in higher concentration in the aqueous humor than when delivered by reference eyedrops (commercial ocular compositions). This result is shown in Fig.1 (page 244, *Cavalli's* publication).

Aqueous humor is different from vitreous humor and is part of the anterior fragment of the eye. Therefore, this effect, which has not been suggested by the *Cavalli* publication, has been disclosed for the first time in the present Application, and has been confirmed with studies performed relating to the filing of present application. A Declaration Under Rule 132 with these data may be prepared and filed if requested by the Examiner.

As already said above, *Schwartz (US 4,904,649)* teaches neither how to administer drugs to the posterior eye, nor how to treat glaucoma. Therefore no suggestion can be envisaged to the

therapeutic effect achieved with the present invention.

Also, the Applicant has observed that the drug distribution to the back part of the eye, has been obtained also by i.v. administration in the marginal ear vein in rabbit, as described above (examples 2-3 page 6-8 of the present Application). This represents a surprising result and it was totally unpredictable.

Regarding the double patenting rejection, the Applicant has not found any basis for such an objection for any of the pending claims, in the cited Application 11/629941. Withdrawal of this rejection is respectfully requested.

In view of Applicant's amendments to the claims and the foregoing arguments and remarks, the present invention and all the claims are not anticipated under 35 U.S.C. 102 but are patentable under 35 U.S.C. 103 over all the prior art applied by the Patent Examiner. Thus, the present patent application

should be considered in condition for allowance.

Respectfully submitted,
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Enclosure: Petition for 3 Month Extension of Time-Small Entity

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to: Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on July 7, 2009.

Amy Klein